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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,439	02/17/2004	Phillip Dan Cook	ISIS-4380US.C1	5764
27180	7590	07/20/2006	EXAMINER	
ISIS PHARMACEUTICALS INC 1896 RUTHERFORD RD. CARLSBAD, CA 92008			FREDMAN, JEFFREY NORMAN	
			ART UNIT	PAPER NUMBER
			1637	
DATE MAILED: 07/20/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/780,439

Applicant(s)

COOK ET AL.

Examiner

Jeffrey Fredman

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)            |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/11/05</u> . | 6) <input type="checkbox"/> Other: ____  |

## DETAILED ACTION

### *Double Patenting*

1. Claims 2-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,753,423.

Claims 1-7 of U.S. Patent No. 6,753,423 teach a method of preferentially targeting a biologically active antisense oligonucleotide to hepatic tissues in a mammal to modulate the expression of a gene in the liver of a mammal, comprising the step of conjugating the oligonucleotide to a cholesteryl moiety and administering the cholesterol-oligonucleotide conjugate to said mammal to achieve said preferential targeting.

2. A method of modulating the expression of a nucleic acid in the hepatic system of a mammal, comprising the step of administering to said mammal a compound to modulate the expression of said nucleic acid, said compound comprising a plurality of linked nucleosides, wherein: each nucleoside includes a ribofuranosyl sugar portion and a base portion; and at least one of said nucleosides bears at a 2'-O-position, a 3'-O-position, or a 5'-O-position a substituent having formula: --R.sub.A --

N(R.sub.1a)(R.sub.1b) where: R.sub.A is alkyl having from 1 to about 10 carbon atoms or (CH.sub.2 --CH.sub.2 --Q).sub.x ; R.sub.1a and .sub.1b, independently, are H, R.sub.2, an amine protecting group or have formula C(X)--R.sub.2, C(X)--R.sub.A -- R.sub.2, C(X)--Q--R.sub.A --R.sub.2, C(X)--Q--R.sub.2 ; and R.sub.2 is cholesterol; X is O or S; each Q is, independently, NH, O, or S; x is 1 to about 200; R.sub.3 is H, R.sub.A, C(O)OH, C(O)OR.sub.A, C(O)R.sub.4, R.sub.A --N.sub.3, or R.sub.A --

NH.sub.2 ; R.sub.4 is Cl, Br, I, SO.sub.2 R.sub.5 or has structure; ##STR3## m is 2 to 7; and R.sub.5 alkyl having 1 to about 10 carbon atoms; wherein at least one of R.sub.1a and R.sub.1b are R.sub.2.

3. A method of preferentially targeting an oligonucleotide to hepatic tissues in a mammal comprising administering to said mammal an oligonucleotide having a cholesteryl moiety conjugated thereto, to preferentially target said oligonucleotide to hepatic tissues in said mammal.

4. The method of claim 3 wherein said cholesteryl moiety is conjugated to said oligonucleotide through an alkylamine tether.

5. The method of claim 3 wherein said cholesteryl moiety is conjugated to said oligonucleotide at the terminal 5'-hydroxyl group of said oligonucleotide.

6. The method of claim 3 wherein said cholesteryl moiety is conjugated to said oligonucleotide at the terminal 3'-hydroxyl group of said oligonucleotide.

7. The method of claim 3 wherein said cholesteryl moiety is conjugated to said oligonucleotide at a 2'-hydroxyl group of said oligonucleotide.

Claims 1-7 of U.S. Patent No. 6,753,423 do not expressly teach using the method in mammals "in need of hepatic gene modulation" but the entire thrust of the claims is designed to target the hepatic system of mammals with antisense compound which are compounds designed to modulate genes in the tissue to which they are directed.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the method of claims 1-7 of U.S. Patent No.

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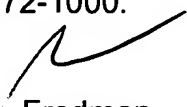
6,753,423 on mammals "in need of hepatic gene modulation" since the claims are entirely directed towards the use of antisense as a therapeutic for modulation of genes.

**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Jeffrey Fredman  
Primary Examiner  
Art Unit 1637

7/18/06